Any obligation not covered by the written description shall be deemed not to have been transferred.

(3) A contract research organization that assumes any obligation of a sponsor shall comply with the specific regulations in this chapter applicable to this obligation and shall be subject to the same regulatory action as a sponsor for failure to comply with any obligation assumed under these regulations. Thus, all references to *sponsor* in this part apply to a contract research organization to the extent that it assumes one or more obligations of the sponsor.

[40 FR 13823, Mar. 27, 1975, as amended at 41 FR 48268, Nov. 2, 1976; 42 FR 15675, Mar. 22, 1977; 50 FR 7517, Feb. 22, 1985; 50 FR 16668, Apr. 26, 1985; 52 FR 8847, Mar. 19, 1987; 54 FR 18280, Apr. 28, 1989; 57 FR 6475, Feb. 25, 1992; 62 FR 40599, July 29, 1997]

PART 514—NEW ANIMAL DRUG APPLICATIONS

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SOURCE: 40 FR 13825, Mar. 27, 1975, unless otherwise noted.

Subpart A—General Provisions

§ 514.1 Applications.

(a) Applications to be filed under section 512(b) of the act shall be submitted in the form described in paragraph (b) of this section. If any part of the application is in a foreign language, an accurate and complete English translation shall be appended to such part. Translations of literature printed in a foreign language shall be accompanied by copies of the original publication. The application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of, and must be countersigned by, an authorized attorney, agent, or official residing or maintaining a place of business within the United States. Pertinent information may be incorporated in, and will be considered as part of, an application on the basis of specific reference to such information, including information submitted under the provisions of §511.1 of this chapter, in the files of the Food and Drug Administration; however, the reference must be specific in identifying the information. Any reference to information furnished by a person other than the applicant may

not be considered unless its use is authorized in a written statement signed by the person who submitted it.

(b) Applications for new animal drugs shall be submitted in triplicate and assembled in the manner prescribed by paragraph (b)(15) of this section, and shall include the following information:

(1) *Identification.* Whether the submission is an original or supplemental application; the name and the address of the applicant; the date of the application; the trade name(s) (if one has been proposed) and chemical name(s) of the new animal drug. Upon receipt, the application will be assigned a number NADA ____, which shall be used for all correspondence with respect to the application.

(2) *Table of contents and summary.* The application shall be organized in a cohesive fashion, shall contain a table of contents which identifies the data and other material submitted, and shall contain a well-organized summary and evaluation of the data in the following form:

(i) Chemistry:

(*a*) Chemical structural formula or description for any new animal drug substance.

(*b*) Relationship to other chemically or pharmacologically related drugs.

(*c*) Description of dosage form and quantitative composition.

(ii) Scientific rationale and purpose the new animal drug is to serve:

(*a*) Clinical purpose.

(*b*) Highlights of laboratory studies: The reasons why certain types of studies were done or omitted as related to the proposed conditions of use and to information already known about this class of compounds. Emphasize any unusual or particularly significant pharmacological effects or toxicological findings.

(*c*) Highlights of clinical studies: The rationale of the clinical study plan showing why types of studies were done, amended, or omitted as related to laboratory studies and prior clinical experience.

(*d*) Conclusions: A short statement of conclusions combining the major points of effectiveness and safety as they relate to the use of the new animal drug.

(3) *Labeling.* Three copies of each piece of all labeling to be used for the article (total of 9).

(i) All labeling should be identified to show its position on, or the manner in which it is to accompany the market package.

(ii) Labeling for nonprescription new animal drugs should include adequate directions for use by the layman under all conditions of use for which the new animal drug is intended, recommended, or suggested in any of the labeling or advertising sponsored by the applicant.

(iii) Labeling for prescription veterinary drugs should bear adequate information for use under which veterinarians can use the new animal drug safely and for the purposes for which it is intended, including those purposes for which it is to be advertised or represented, in accord with §201.105 of this chapter.

(iv) All labeling for prescription or nonprescription new animal drugs shall be submitted with any necessary use restrictions prominently and conspicuously displayed.

(v) Labeling for new animal drugs intended for use in the manufacture of medicated feeds shall include:

(*a*) Specimens of labeling to be used for such new animal drug with adequate directions for the manufacture and use of finished feeds for all conditions for which the new animal drug is intended, recommended, or suggested in any of the labeling, including advertising, sponsored by the applicant. Ingredient labeling may utilize collective names as provided in §501.110 of this chapter.

(*b*) Representative labeling proposed to be used for Type B and Type C medicated feeds containing the new animal drug.

(vi) Draft labeling may be submitted for preliminary consideration of an application. Final printed labeling will ordinarily be required prior to approval of an application. Proposed advertising for veterinary prescription drugs may be submitted for comment or approval.

(4) *Components and composition.* A complete list of all articles used for production of the new animal drug including a full list of the composition of each article:

(i) A full list of the articles used as components of the new animal drug. This list should include all substances used in the synthesis, extraction, or other method of preparation of any new animal drug and in the preparation of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. Each component should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary name is used, it should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed component may be specified.

(ii) A full statement of the composition of the new animal drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the new animal drug in the form in which it is to be distributed (for example, amount per tablet or milliliter) and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variation may be specified.

(iii) If it is a new animal drug produced by fermentation:

(*a*) Source and type of microorganism used to produce the new animal drug.

(*b*) Composition of media used to produce the new animal drug.

(*c*) Type of precursor used, if any, to guide or enhance production of the antibiotic during fermentation.

(*d*) Name and composition of preservative, if any, used in the broth.

(*e*) A complete description of the extraction and purification processes including the names and compositions of the solvents, precipitants, ion exchange resins, emulsifiers, and all other agents used.

(*f*) If the new animal drug is produced by a catalytic hydrogenation process (such as tetracycline from chlortetracycline), a complete description of each chemical reaction with graphic formulas used to produce the new animal drug, including the names of the catalyst used, how it is removed, and how the new animal drug is extracted and purified.

(5) *Manufacturing methods, facilities, and controls.* A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the new animal drug. This description should include full information with respect to any new animal drug in sufficient detail to permit evaluation of the adequacy of the described methods of manufacture, processing, and packing, and the described facilities and controls to determine and preserve the identity, strength, quality, and purity of the new animal drug, and the following:

(i) If the applicant does not himself perform all the manufacturing, processing, packaging, labeling, and control operations for any new animal drug, he shall: Identify each person who will perform any part of such operations and designate the part; and provide a signed statement from each such person fully describing, directly or by reference, the methods, facilities, and controls he will use in his part of the operation. The statement shall include a commitment that no changes will be made without prior approval by the Food and Drug Administration, unless permitted under § 514.8.

(ii) A description of the qualifications, including educational background and experience, of the technical and professional personnel who are responsible for assuring that the new animal drug has the identity, strength, quality, and purity it purports or is represented to possess, and a statement of their responsibilities.

(iii) A description of the physical facilities including building and equipment used in manufacturing, processing, packaging, labeling, storage, and control operations.

(iv) The methods used in the synthesis, extraction, isolation, or purification of any new animal drug. When the specifications and controls applied to such new animal drugs are inadequate in themselves to determine its identity, strength, quality, and purity,

the methods should be described in sufficient detail, including quantities used, times, temperature, pH, solvents, etc., to determine these characteristics. Alternative methods or variations in methods within reasonable limits that do not affect such characteristics of the new animal drug may be specified. A flow sheet and indicated equations should be submitted when needed to explain the process.

(v) Precautions to insure proper identity, strength, quality, and purity of the raw materials, whether active or not, including:

(*a*) The specifications for acceptance and methods of testing for each lot of raw material.

(*b*) A statement as to whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.

(vi) The instructions used in the manufacturing, processing, packaging, and labeling of each dosage form of the new animal drug, including:

(*a*) The method of preparation of the master formula records and individual batch records and the manner in which these records are used.

(*b*) The number of individuals checking weight or volume of each individual ingredient entering into each batch of the new animal drug.

(*c*) A statement as to whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and, if so, at what stage and by whom it is done.

(*d*) The precautions used in checking the actual package yield produced from a batch of the new animal drug with the theoretical yield. This should include a description of the accounting for such items as discards, breakage, etc., and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

(*e*) The precautions used to assure that each lot of the new animal drug is packaged with the proper label and labeling, including provisions for labeling storage and inventory control.

(*f*) Any special precautions used in the operations.

(vii) The analytical controls used during the various stages of the manufacturing, processing, packaging, and labeling of the new animal drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components.

(*a*) A description of practicable methods of analysis of adequate sensitivity to determine the amount of the new animal drug in the final dosage form should be included. The dosage form may be a finished pharmaceutical product, a Type A medicated article, a Type B or a Type C medicated feed, or a product for use in animal drinking water. Where two or more active ingredients are included, methods should be quantitative and specific for each active ingredient.

(b) If the article is one that is represented to be sterile, the same information with regard to the manufacturing, processing, packaging, and the collection of samples of the drug should be given for sterility controls. Include the standards used for acceptance of each lot of the finished drug.

(viii) An explanation of the exact significance of any batch control numbers used in the manufacturing, processing, packaging, and labeling of the new animal drug, including such control numbers that may appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

(ix) Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug package to assure their suitability for the intended use.

(x) A complete description of, and data derived from, studies of the stability of the new animal drug in the final dosage form, including information showing the suitability of the analytical methods used. A description of

any additional stability studies underway or planned. Stability data for the finished dosage form of the new animal drug in the container in which it is to be marketed, including any proposed multiple dose container, and, if it is to be put into solution at the time of dispensing, for the solution prepared as directed. If the new animal drug is intended for use in the manufacture of Type C medicated feed as defined in § 558.3 of this chapter, stability data derived from studies in which representative formulations of the medicated feed articles are used. Similar data may be required for Type B medicated feeds as determined by the Food and Drug Administration on a case-by-case basis. Expiration dates shall be proposed for finished pharmaceutical dosage forms and Type A medicated articles. If the data indicate that an expiration date is needed for Type B or Type C medicated feeds, the applicant shall propose such expiration date. If no expiration date is proposed for Type B or Type C medicated feeds, the applicant shall justify its absence with data.

(xi) Additional procedures employed which are designed to prevent contamination and otherwise assure proper control of the product. An application may be refused unless it includes adequate information showing that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the new animal drug are adequate to preserve its identity, strength, quality, and purity in conformity with good manufacturing practice and identifies each establishment, showing the location of the plant conducting these operations.

(6) *Samples.* Samples of the new animal drug and articles used as components and information concerning them may be requested by the Center for Veterinary Medicine as follows:

(i) Each sample shall consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory test procedures described in the application to determine compliance with its control specifications for identity and assays. Each of the samples submitted shall be appropriately packaged and labeled to preserve its characteristics, to identify the material and the quantity in each subdivision of the sample, and to identify each subdivision with the name of the applicant and the new animal drug application to which it relates. Included are:

(a) A sample or samples of any reference standard and blank used in the procedures described in the application for assaying each new animal drug and other assayed components of the finished new animal drug.

(b) A representative sample or samples of each strength of the finished dosage form proposed in the application and employed in the clinical investigations and a representative sample or samples of each new animal drug from the batch(es) employed in the production of such dosage form.

(c) A representative sample or samples of finished market packages of each strength of the dosage form of the new animal drug prepared for initial marketing and, if any such sample is not from a representative commercial-scale production batch, such a sample from a representative commercial-scale production batch, and a representative sample or samples of each new animal drug from the batch(es) employed in the production of such dosage form, provided that in the case of new animal drugs marketed in large packages the sample should contain only three times a sufficient quantity of the new animal drug to allow for performing the control tests for drug identity and assays.

(ii) The following information shall be included for the samples when requested:

(a) For each sample submitted, full information regarding its identity and the origin of any new animal drug contained therein (including a statement whether it was produced on a laboratory, pilot-plant, or full-production scale) and detailed results of all laboratory tests made to determine the identity, strength, quality, and purity of the batch represented by the sample, including assays.

(b) For any reference standard submitted, a complete description of its preparation and the results of all laboratory tests on it. If the test methods used differed from those described in the application, full details of the

methods employed in obtaining the reporting results.

(7) *Analytical methods for residues.* Applications shall include a description of practicable methods for determining the quantity, if any, of the new animal drug in or on food, and any substance formed in or on food because of its use, and the proposed tolerance or withdrawal period or other use restrictions to ensure that the proposed use of this drug will be safe. When data or other adequate information establish that it is not reasonable to expect the new animal drug to become a component of food at concentrations considered unsafe, a regulatory method is not required.

(i) The kind of information required by this subdivision may include: Complete experimental protocols for determining drug residue levels in the edible products, and the length of time required for residues to be eliminated from such products following the drug's use; residue studies conducted under appropriate (consistent with the proposed usage) conditions of dosage, time, and route of administration to show levels, if any, of the drug and/or its metabolites in test animals during and upon cessation of treatment and at intervals thereafter in order to establish a disappearance curve; if the drug is to be used in combination with other drugs, possible effects of interaction demonstrated by the appropriate disappearance curve or depletion patterns after drug withdrawal under appropriate (consistent with the proposed usage) conditions of dosage, time, and route of administration; if the drug is given in the feed or water, appropriate consumption records of the medicated feed or water and appropriate performance data in the treated animal; if the drug is to be used in more than one species, drug residue studies or appropriate metabolic studies conducted for each species that is food-producing. To provide these data, a sufficient number of birds or animals should be used at each sample interval. Appropriate use of labeled compounds (e.g. radioactive tracers), may be utilized to establish metabolism and depletion curves. Drug residue levels ordinarily should be determined in muscle, liver, kidney, and fat and where applicable, in skin, milk, and eggs (yolk and egg white). As a part of the metabolic studies, levels of the drug or metabolite should be determined in blood where feasible. Samples may be combined where necessary. Where residues are suspected or known to be present in litter from treated animals, it may be necessary to include data with respect to such residues becoming components of other agricultural commodities because of use of litter from treated animals.

(ii) A new animal drug that has the potential to contaminate human food with residues whose consumption could present a risk of cancer to people must satisfy the requirements of subpart E of part 500 of this chapter.

(8) *Evidence to establish safety and effectiveness.* (i) An application may be refused unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the new animal drug is safe and effective for use as suggested in the proposed labeling.

(ii) An application may be refused unless it includes substantial evidence of the effectiveness of the new animal drug as defined in §514.4.

(iii) An application may be refused unless it contains detailed reports of the investigations, including studies made on laboratory animals, in which the purpose, methods, and results obtained are clearly set forth of acute, subacute, and chronic toxicity, and unless it contains appropriate clinical laboratory results related to safety and efficacy. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the raw data are available in the application.

(iv) All information pertinent to an evaluation of the safety and effectiveness of the new animal drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commercial marketing (for example, outside the United States), or reports in the scientific literature, both favorable and unfavorable, involving the new animal drug that is the subject of the application and related new animal drugs shall be submitted. An adequate summary may be acceptable in lieu of

a reprint of a published report that only supports other data submitted. Include any evaluation of the safety or effectiveness of the new animal drug that has been made by the applicant's veterinary or medical department, expert committee, or consultants.

(v) If the new animal drug is a combination of active ingredients or animal drugs, an application may be refused unless it includes substantial evidence of the effectiveness of the combination new animal drug as required in § 514.4.

(vi) An application shall include a complete list of the names and post office addresses of all investigators who received the new animal drug. This may be incorporated in whole or in part by reference to information submitted under the provisions of § 511.1 of this chapter.

(vii) Explain any omission of reports from any investigator to whom the investigational new animal drug has been made available. The unexplained omission of any reports of investigations made with the new animal drug by the applicant or submitted to him by an investigator or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources that would bias an evaluation of the safety of the new animal drug or its effectiveness in use, constitutes grounds for the refusal or withdrawal of the approval of an application.

(viii) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization, the application is required to include a statement containing the name and address of the contract research organization, identifying the clinical study, and listing the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer—in lieu of a listing of the specific obligations transferred—may be submitted.

(ix) If original subject records were audited or reviewed by the sponsor in the course of monitoring any clinical study to verify the accuracy of the case reports submitted to the sponsor, a list identifying each clinical study so audited or reviewed.

(9) *Veterinary feed directive.* Three copies of a veterinary feed directive (VFD) must be submitted in the format described under § 558.6(a)(4) of this chapter.

(10) *Supplemental applications.* If it is a supplemental application, full information shall be submitted on each proposed change concerning any statement made in the approved application.

(11) *Applicant's commitment.* It is understood that the labeling and advertising for the new animal drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application and if the article is a prescription new animal drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the new animal drug will also contain, in the same language and emphasis, information for its use including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant hazards, contraindications, side effects, and precautions contained in the labeling which is part of this application. It is understood that all representations in this application apply to the drug produced until changes are made in conformity with § 514.8.

(12) *Additional commitments.* (i) New animal drugs as defined in § 510.3 of this chapter, intended for use in the manufacture of animal feeds in any State will be shipped only to persons who may receive such drugs in accordance with § 510.7 of this chapter.

(ii) The methods, facilities, and controls described under item 5 of this application conform to the current good manufacturing practice regulations in subchapter C of this chapter.

(iii) With respect to each nonclinical laboratory study contained in the application, either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a

brief statement of the reason for the noncompliance.

(13) [Reserved]

(14) *Environmental assessment.* The applicant is required to submit either a claim for categorical exclusion under §25.30 or §25.33 of this chapter or an environmental assessment under §25.40 of this chapter.

(15) *Assembling and binding the application.* Assemble and bind an original and two copies of the application as follows:

(i) Bind the original or ribbon copy of the application as copy No. 1.

(ii) Bind two identical copies as copy No. 2 and copy No. 3.

(iii) Identify each front cover with the name of the applicant, new animal drug, and the copy number.

(iv) Number each page of the application sequentially in the upper right hand corner or in another location so that the page numbers remain legible after the application has been bound, and organize the application consistent with paragraphs (b) (1) through (14) of this section. Each copy should bear the same page numbering, whether sequential in each volume or continuous and sequential throughout the application.

(v) Include complete labeling in each of the copies. It is suggested that labeling be identified by date of printing or date of preparation.

(vi) Submit separate applications for each different dosage form of the drug proposed. Repeating basic information pertinent to all dosage forms in each application is unnecessary if reference is made to the application containing such information. Include in each application information applicable to the specific dosage form, such as labeling, composition, stability data, and method of manufacture.

(vii) Submit in folders amendments, supplements, and other correspondence sent after submission of an original application. The front cover of these submissions should be identified with the name of the applicant, new animal drug, copy number, and the new animal drug application number, if known.

(c) When a new animal drug application is submitted for a new animal drug which has a stimulant, depressant, or hallucinogenic effect on the central nervous system, if it appears that the drug has a potential for abuse, the Commissioner shall forward that information to the Attorney General of the United States.

(d) *Minor use applications.* Applications for minor use new animal drugs:

(1) *Definitions.* For the purpose of this section:

(i) *Minor use* means the use of: (*a*) New animal drugs in minor animal species, or (*b*) new animal drugs in any animal species for the control of a disease that (*1*) occurs infrequently or (*2*) occurs in limited geographic areas.

(ii) *Minor species* means animals other than cattle, horses, swine, chickens, turkeys, dogs, and cats.

(2) *Animal safety, effectiveness, human food safety, and environmental considerations.* Guidance documents for the preparation and submission of data to satisfy the requirements of section 512 of the act regarding animal safety, effectiveness, human food safety, and environmental considerations for new animal drugs intended for a *minor use* (as defined in paragraph (d)(1)(i) of this section) are available from the Industry Information Staff (HFV–11), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

(i) *Animal safety and effectiveness.* Where the guidance documents do not specifically provide for a particular *minor use*, the Center for Veterinary Medicine, upon request, will advise interested persons on the effectiveness and animal safety data regarding the minor use that will be needed to satisfy the requirements of section 512 of the act. Where scientifically appropriate, the Center for Veterinary Medicine will allow the use of animal models and the extrapolation of data from a major species to a minor species to satisfy the requirements of the act.

(ii) *Human food safety and environmental considerations.* These guidance documents do not specifically provide for a particular *minor use.* Therefore, the Center for Veterinary Medicine will, upon request, advise interested persons of the data that will be needed. Where scientifically appropriate, the Center for Veterinary Medicine will allow the extrapolation of data from a

major species to a minor species to satisfy the requirements of the act.

[40 FR 13825, Mar. 27, 1975]

EDITORIAL NOTE: For FEDERAL REGISTER citations affecting §514.1, see the List of CFR Sections Affected, which appears in the Finding Aids section of the printed volume and on GPO Access.

§ 514.3 Definitions.

The definition and interpretation of terms contained in this section apply to those terms as used throughout subchapter E.

Adverse drug experience is any adverse event associated with the use of a new animal drug, whether or not considered to be drug related, and whether or not the new animal drug was used in accordance with the approved labeling (i.e., used according to label directions or used in an extralabel manner, including but not limited to different route of administration, different species, different indications, or other than labeled dosage). Adverse drug experience includes, but is not limited to:

(1) An adverse event occurring in animals in the course of the use of an animal drug product by a veterinarian or by a livestock producer or other animal owner or caretaker.

(2) Failure of a new animal drug to produce its expected pharmacological or clinical effect (lack of expected effectiveness).

(3) An adverse event occurring in humans from exposure during manufacture, testing, handling, or use of a new animal drug.

ANADA is an abbreviated new animal drug application including all amendments and supplements.

Applicant is a person or entity who owns or holds on behalf of the owner the approval for an NADA or an ANADA, and is responsible for compliance with applicable provisions of the act and regulations.

Increased frequency of adverse drug experience is an increased rate of occurrence of a particular serious adverse drug event, expected or unexpected, after appropriate adjustment for drug exposure.

NADA is a new animal drug application including all amendments and supplements.

Nonapplicant is any person other than the applicant whose name appears on the label and who is engaged in manufacturing, packing, distribution, or labeling of the product.

Potential applicant means any person:

(1) Intending to investigate a new animal drug under section 512(j) of the Federal Food, Drug, and Cosmetic Act (the act),

(2) Investigating a new animal drug under section 512(j) of the act,

(3) Intending to file a new animal drug application (NADA) or supplemental NADA under section 512(b)(1) of the act, or

(4) Intending to file an abbreviated new animal drug application (ANADA) under section 512(b)(2) of the act.

Presubmission conference means one or more conferences between a potential applicant and FDA to reach a binding agreement establishing a submission or investigational requirement.

Presubmission conference agreement means that section of the memorandum of conference headed ''Presubmission Conference Agreement'' that records any agreement on the submission or investigational requirement reached by a potential applicant and FDA during the presubmission conference.

Product defect/manufacturing defect is the deviation of a distributed product from the standards specified in the approved application, or any significant chemical, physical, or other change, or deterioration in the distributed drug product, including any microbial or chemical contamination. A manufacturing defect is a product defect caused or aggravated by a manufacturing or related process. A manufacturing defect may occur from a single event or from deficiencies inherent to the manufacturing process. These defects are generally associated with product contamination, product deterioration, manufacturing error, defective packaging, damage from disaster, or labeling error. For example, a labeling error may include any incident that causes a distributed product to be mistaken for, or its labeling applied to, another product.

Serious adverse drug experience is an adverse event that is fatal, or life-threatening, or requires professional